Remarks

Reconsideration of this application as amended is requested.

Claims 1 through 19 and 21 are now in this application. Applicants' provisional election of Species 1 ("OPS"), includes the remaining independent claims 1, 2, 4, and 21, and all the remaining dependent claims depending therefrom (claims 5-19), as was discussed briefly with the Examiner during a recent interview on another application.

Claims 1, 2 and 4 have been amended to more fully describe the invention and to more particularly point out its novel features. Support for these amendments can be found, for example, on pages 12 and 13 through line 11, on page 23, lines 24 through 29, throughout the Specification, and in the claims as originally submitted.

Claim 3 has been deleted. Subsequent experiments conducted since the filing of this application have indicated that the mature form of OP-1 is slightly larger than was believed at the time of filing this application. New data indicates that the mature form's N terminal amino acid is the serine residue (S) encoded by TCC at position 925-927 of the DNA of Fig. 1B-1. The correct structure of the mature form

will be included in a continuation-in-part of the present application, to be filed shortly. The Specification has been amended by deletion of text which could be construed as inconsistent with this recent data so as to avoid confusion.

Claims 5-19 have been amended to remove their dependency from claim 3, now deleted.

Claims 5, 6, 8 and 9 have been amended to remove the redundant term "apparent".

Claims 12 and 13 have been amended to more accurately describe the claimed amino acid sequences.

Claim 21 has been amended and made independent of non-elected claim 20 from which it previously depended.

The Specification also has been amended to correct minor typographical errors, and to remove extraneous matter.

At the outset, the undersigned attorney wishes to thank Eaminer Nutter for his time and consideration during the interview which took place at the Patent Office on June 7, 1990. The substance of the interview is described in the Examiner Interview Summary Record.

Applicants' invention is directed to novel recombinantly produced osteogenic proteins which, when associated with a matrix and implanted in a mammalian body, can induce at the locus of the implant the full developmental cascade of endochondral bone formation and bone marrow differentiation. The novel protein of Applicants' invention comprises a dimer, i.e., a protein comprising two chains or subunits joined together by disulfide bonds. One subunit of the dimer is OP-1, or a sequence sufficiently duplicative of OP-1 such that when the subunits are disulfide bonded to produce a dimeric species, the dimerized pair of polypeptide chains will have a conformation capable of inducing endochondral bone formation when implanted in a mammal in association with a matrix. Pursuant to Applicants' invention, useful osteogenic proteins can be native form proteins or fusion proteins comprising the native form sequence. They may also comprise analogs of the active regions, including forms having varying glycosylation patterns, varying N-termini, and various truncated or mutated forms, designed in accordance with Applicants' disclosure. Moreover, active dimeric species can comprise homodimers or heterodimers of any of these forms of OP-1.

Applicants' invention, in its broadest aspects, is based on the discovery of the most fundamental amino acid sequence structure required for osteogenic activity. The

present invention is a continuation of co-pending U.S. Application Serial Nos. 179,406, 232,630, and 315,342, wherein Applicants disclose how to make substantially pure osteogenic protein having a half maximum bone-inducing activity of at least about 1-2 ng per mg of the matrix, as well as how to make active, unglycosylated osteogenic protein. Elucidation of the amino acid sequence and investigation of the properties and structure of the native form osteogenic protein has allowed Applicants to isolate the DNA sequences encoding each of the polypeptides of the osteogenic protein's two chain sequence. The DNA sequences encode novel polypeptides designated as OP-1, and CBMP2. The DNA sequences of CBMP2 correspond to a sub-region of the BMP-2 cDNA sequences disclosed in WO88/00205. The sequence of OP-1 has never before been described as far as Applicants are aware.

In addition, discovery of the amino acid residues and linear sequence minimally required for osteogenic activity permitted the inventors to develop a rational design for non-native form proteins, i.e., forms never before known in nature, and capable of inducing bone formation (and/or cartilage). As far as Applicants are aware, these constructs, disclosed in U.S. 315,342, constitute the first instance of the design of a functional, active protein without preexisting knowledge of the active region of a native form nucleotide or amino acid sequence.

The recombinantly produced OP-1 proteins disclosed in the present Application are active as homodimers or heterodimers with CBMP2 or non-native analogs. In view of this disclosure, skilled genetic engineers can isolate genes from cDNA or genomic libraries which encode appropriate amino acid sequences, or construct DNAs from oligonucleotides, and then express them in various types of host cells including both prokaryotes and eucaryotes, to produce large quantities of active proteins capable of inducing bone formation in mammals, including humans, and having a high specific activity.

The claims presently stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants have amended the claims in response to the §112 rejections, and respectfully traverse these rejections, to the extent that they are applied to the claims as amended.

The Examiner has deemed the claims to be "vague and confusing, since only one of the proteins of the dimeric pair is provided." Applicants respectfully traverse this rejection.

Applicants' invention is directed to active forms of osteogenic protein comprising the OP-1 sequence. As amended, the claims are directed to recombinantly produced proteins

comprising a pair of disulfide bonded subunits, having a conformation such that the protein is capable of inducing endochrondal bone formation when disposed within a matrix and implanted in a mammal, and where at least one of the subunits includes the active region of OP-1. The limiting aspects of the claims are believed to be commensurate with Applicants' contribution to the art. As disclosed in the Specification, OP-1 DNA can be expressed to form various active dimers, whether the DNA sequence comprises the intact gene, truncated forms of the gene, OP-1 muteins, or fusion proteins comprising the active region of OP-1. The dimers may be true homodimers of OP-1, or they may include heterodimers comprising different forms of OP-1. OP-1 is also active as a true heterodimer with CBMP2 or with completely biosynthetic non-native analogs (e.g., COP5, COP7, and COP16, see p. 42 of the Specification and WO89/01469). Applicants respectfully submit that the claims, as amended, appropriately describe that subject matter which Applicants regard as the invention, that the Specification is sufficient to enable one of ordinary skill in the art to make and use the invention without undue experimentation, and that the claims as amended comply fully with the second paragraph of 35 USC §112.

Claims 3, 12 and 13 are rejected as "the starred residues, which term is not art-recognized, are many and intended cleavage sites cannot be clearly ascertained."

Applicants have deleted claim 3 and amended claims 12 and 13 to remove the starred residues and their description in the claims as defining a potential cleavage site. As amended, claims 12 and 13 are believed to overcome the Examiner's rejections and to be in condition for allowance.

Claim 21 is rejected as reciting a protein without giving any intended aspects of that protein. It has now been amended and defined specifically with reference to the DNA sequence of Fig. 1B of the drawing.

The Examiner wishes to know the intended scope of the matrix involved. The Examiner deems that "nothing is recited in the claims which would enable one of ordinary skill to practice and/or produce such a matrix." Applicants respectfully traverse this rejection. The Examiner is directed to page 34, lines 1 through 20 of the Specification where the characteristics required of matrix materials for use in association with the osteogenic proteins of this invention are described; to page 33, lines 1 through 9, where suitable matrix materials are disclosed; and to pages 35 through 39, where the preparation of allogenic and xenogenic bone matrices are disclosed. The Examiner is further directed to pages 39 through 40 of the Specification, where several methods for making an osteogenic device (osteogenic protein dispersed in

matrix) are disclosed. Applicants submit that the metes and bounds of the matrix are adequately enabled by the Specification. Furthermore, the protein of the invention also may be used with matrices disclosed in the prior art.

The claims presently stand rejected under 35 USC §103 as unpatentable over Urist or Nathan taken in view of Wang. The Examiner states that Urist and Nathan both "teach isolation of bone morphogenic proteins which are deemed to embrace those of the instant claims with possibly only minor differences from those proteins recited in the instant claims". The Examiner also states that the patent to Wang

> "...teaches the conventionality of recombinant techniques to produce proteins possessing osteogenic capabilities as is disclosed in the instant Specification. Manipulation of the products as resulting from these techniques is known in the art and is taught in the reference."
>
> And: "The instant claims are drawn to proteins/polypeptides per se. Derivation of these proteins/polypeptides are irrelevant, since the claims are drawn to the product, per se. Nothing in the record indicates any substantial patentable differences thereover. Thus, at the time the invention (protein/polypeptides) was made, the claimed combination would have been obvious to one having an ordinary skill in the art."

Applicants respectfully traverse this rejection. Wang is directed to the recombinant production of four (purported) bone inductive factors BMP-1, BMP-2 (BMP-2A), BMP-3, and BMP-4 (BMP-2B). Wang teaches isolating the genomic

and cDNA sequences for these proteins, but has expressed, purified and tested only one protein (BMP-1) for bone forming activity, and the test failed. The recombinant protein is shown only to have "cartilage-like nodules at 7 days post implantation." (see p.55, line 2). Subsequent in vivo assays performed on human BMP-2, BMP-3 and BMP-4 protein are disclosed in a later publication by this group. These also failed to induce bone formation. (Wozney et al., (1988) Science 242:1528-1534, pp.1531, 1532.) Only after Applicants' published PCT application (WO89/10459) became available were Wang et al. able to express one of the genes (BMP2-A) to generate low specific activity protein (Wang et al., (1990) PNAS 87:2220-2224.)

Applicants respectfully submit that Wang fails to disclose that any of the polypeptide sequences comprise a protein which exhibits endochondral bone forming activity. Moreover, Applicants submit that it is unobvious how to modify any of the substances disclosed in Wang to obtain the active osteogenic protein of Applicant's invention, and that Applicants' invention is not inherently made by following Wang's teachings.

Finally, even if Wang did teach the "conventionality of recombinant techniques to produce proteins possessing

osteogenic capabilities," none of the four DNA sequences set forth in the applied Wang reference correspond to the OP-1 sequences that Applicants have identified, expressed, and shown to have osteogenic activity as disclosed in the present application. Applicants submit that, following the protocol disclosed in Wang, one would not obtain the OP-1 sequences of Applicants' invention nor is there anything in the Wang reference that teaches or suggests how to obtain these sequences.

Applicants submit that none of the secondary references overcomes the deficiencies of the primary reference. Nathan discloses a composition suitable for inductive bone implants comprising a carrier having a percentage of non-fibrillar collagen and a partially purified osteogenic factor defined only as purified sufficiently to be hypoimmunogenic for xenogenic implants (see col.2, lines 64-65; col. 10, line 29; and claim 1.) Others in the art have shown that partially purified osteogenic extracts are active cross-species (see, for example, Sampath et al. (1983), PNAS 80: pp. 6591-6595). Moreover, U.S. 4,774,228 (a division of U.S. Ser. No. 630,938, which is cited in Nathan as disclosing futher purification of the osteogenic factor, and which is now abandoned) discloses the isolation of a dimer having a molecular weight of 26kD and an amino acid sequence

different from that encoded by the OP-1 gene. Moreover, this protein is shown only to have chondrogenic activity, and then requires the presence of TGF-ß.

Similarly, Urist discloses a partially purified osteogenic factor or "bone morphogenic protein" (BMP) defined, in its most pertinent aspects, as having a molecular weight "within the range of 10,000-100,000" (see the Abstract of the Disclosure and claim 1). The bioassay comprising this extract requires 1 mg of extract and six months for complete remodeling to repair a bone defect. By contrast, Applicant's osteogenic proteins are defined by precise molecular weights and by DNA and amino acid sequences.

Applicants respectfully submit that nothing in Nathan or Urist discloses the OP-1 protein or any of the amino acid or DNA sequences of this invention, nor do they suggest or teach how to obtain any of these sequences. Further, even if the impure extracts of Nathan or Urist did comprise OP-1, the courts have held consistently that a purified compound can constitute statutory, novel, nonobvious subject matter patentably distinct from prior art disclosing another, less pure form of the compound, provided that the differences in form or purity are not disclosed or rendered obvious by the prior art. (See In re Cofer, 148 USPQ 268 (CCPA, 1966); In re

Bergstrom and Sjovall, 166 USPQ 256 (CCPA, 1970); In re Irani and Moedritzer, 166 USPQ 24 (CCPA, 1970); and In re Kratz and Strasburger, 201 USPQ 71 (CCPA, 1979)). In this case, the art has attempted for many years without success to obtain the active moiety of osetogenic activity. By following Applicants' teachings, that goal is realized.

In in re Irani and Moedritzer, where the purified compound depended on a small modification of an existing protocol, the court upheld the patentability of the compound stating "(o)bviousness...must not be judged in hindsight, and a "little modification" can be a most unobvious one." (p.27)

In ex parte Stern 13 USPQ 1379 (1989) Appellant claimed the purified protein IL-2 and defined it in terms of "heretofore unascertained properties which include specific activity and amino acid composition." The Board of Appeals determined that the degree of purity alone may be sufficient to warrant a patentably distinct protein as "...(i)t is clear from the record that IL-2 is known to enjoy biological activity...[and] [s]killed workers in this particular art have sought to purify IL-2 to homogeneity and apparently not succeeded." (Ex parte Stern, 13 USPQ 1379, 1381 (1989)).

Applicants hold that their claimed invention is distinct from and unobvious over Urist or Nathan taken in view of Wang, and therefore is free from the prior art.

On the basis of the above amendments and remarks, reconsideration and allowance of the Application and the claims is requested.

Respectfully submitted,

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